

Receptor pre-clustering and T cell responses: insights into molecular mechanisms

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Abstract-

T cell activation, initiated by T cell receptor (TCR) mediated recognition of pathogen-derived peptides presented by major histocompatibility complex class I or II molecules (pMHC), shows exquisite specificity and sensitivity, even though the TCR-pMHC binding interaction is of low affinity. Recent experimental work suggests that TCR pre-clustering may be a mechanism via which T cells can achieve such high sensitivity. The unresolved stoichiometry of the TCR makes TCR-pMHC binding and TCR triggering, an open question. We formulate a mathematical model to characterize the pre-clustering of T cell receptors (TCRs) on the surface of T cells, motivated by the experimentally observed distribution of TCR clusters on the surface of naive and memory T cells. We extend a recently introduced stochastic criterion to compute the timescales of T cell responses, assuming that ligand-induced cross-linked TCR is the minimum signaling unit. We derive an approximate formula for the mean time to signal initiation. Our results show that pre-clustering reduces the mean activation time. However, additional mechanisms favoring the existence of clusters are required to explain the difference between naive and memory T cell responses. We discuss the biological implications of our results, and both the compatibility and complementarity of our approach with other existing mathematical models.

Index Terms- T cell receptor, clustering, stochastic dynamics, signaling, naive T cells, memory T cells

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